CLAIMS

What is claimed is:

1. A method of diagnosing susceptibility to a stroke in an individual, comprising screening for an at-risk haplotype in the phosphodiesterase 4D gene that is more frequently present in an individual susceptible to stroke compared to a healthy individual, wherein the at-risk haplotype increases risk of stroke significantly.

2. The method of claim 1 wherein the significant increase is at least about 20%.

3. The method of claim 1 wherein the significant increase is identified as an odds ratio of at least about 1.2.

4. A method of diagnosing susceptibility to stroke in an individual, comprising screening for an at-risk haplotype in the phosphodiesterase 4D gene that is more frequently present in an individual susceptible to stroke (affected), compared to the frequency of its presence in a healthy individual (control), wherein the presence of the at-risk haplotype is indicative of a susceptibility to stroke.

5. The method of Claim 4 wherein the at risk haplotype 1 is characterized by the presence of G at nucleic acid position 142780, relative to SEQ ID NO: 1 and allele 0 of microsatellite marker AC0088181-1.

6. The method of Claim 4 wherein the at risk haplotype 2 is characterized by the presence of G T A A C C A C G A A C T T A T T G A A T T T G A A at nucleic acid postions: 142780, 135112, 132562, 131865, 129361, 129360, 125304, 123426, 123312, 120628, 118914, 111781, 111252, 109301, 107849, 105225, 104552, 102977, 100795, 99035, 88614, 88456, 83119, 82244, 80127,

78552, relative to SEQ ID NO: 1 and allele 0 of microsatellite marker AC0088181-1.

7. The method of Claim 4 wherein the at risk haplotype 3 is characterized by the presence of A A C A A at nucleic acid positions 138806, 131865, 129361, 120628, 91470, relative to SEQ ID NO: 1.

8. The method of Claim 4 wherein screening for the presence of an at-risk haplotype within or near PDE4D that significantly correlates with haplotype 1 or stroke susceptibility.

9. The method of Claim 4 wherein screening for the presence of an at-risk haplotype within or near PDE4D that significantly correlates with haplotype 2 or stroke susceptibility.

10. The method of Claim 4 wherein screening for the presence of an at-risk haplotype within or near PDE4D that significantly correlates with haplotype 3 or stroke susceptibility.

11. The method of Claim 4 wherein screening for the presence of an at-risk haplotype in the phosphodiesterase 4D gene comprises enzymatic amplification of nucleic acid from said individual.

12. The method of Claim 11 wherein the nucleic acid is DNA.

13. The method of Claim 12 wherein the DNA is mammalian.

14. The method of Claim 13 wherein the DNA is human.

15. The method of Claim 4 wherein screening for the presence of an at-risk haplotype in the phosphodiesterase 4D gene comprises:

(a) obtaining material containing nucleic acid from the individual;

(b) amplifying said nucleic acid; and

(c) determining the presence or absence of an at-risk haplotype in said amplified nucleic acid.

16. The method of Claim 15 wherein determining the presence of an at-risk haplotype is performed by electrophoretic analysis.

17. The method of Claim 15 wherein determining the presence of an at-risk haplotype is performed by restriction length polymorphism analysis.

18. The method of Claim 15 wherein determining the presence of an at-risk haplotype is performed by sequence analysis.

19. The method of Claim 15 wherein determining the presence of an at-risk haplotype is performed by hybridization analysis.

20. A kit for diagnosing susceptibility to stroke in an individual comprising: primers for nucleic acid amplification of a region of the phosphodiesterase 4D gene comprising an at-risk haplotype.

21. The kit of Claim 20 wherein the primers comprise a segment of nucleic acids of length suitable for nucleic acid amplification a single nucleotide polymorphism at nucleic acid position 142780 respectively, relative to SEQ ID NO: 1 and allele 0 of microsatellite marker AC0088181-1.

22. The kit of Claim 20 wherein the primers comprise a segment of nucleic acids of length suitable for nucleic acid amplification, selected from the group consisting of: single nucleotide polymorphism or microsatellite marker at nucleic acid position 142780, 135112, 132562, 131865, 129361, 129360, 125304, 123426, 123312, 120628, 118914, 111781, 111252, 109301, 107849, 105225, 104552, 102977, 100795, 99035, 88614, 88456, 83119, 82244, 80127, 78552, relative to SEQ ID NO: 1, allele 0 of microsatellite marker AC0088181-1.
and combinations thereof.

23. The kit of Claim 20 wherein the primers comprise a segment of nucleic acids of length suitable for nucleic acid amplification, selected from the group consisting of: single nucleotide polymorphism at nucleic acid position at nucleic acid position 138806, 131865, 129361, 120628, 91470, relative to SEQ ID NO: 1 and combinations thereof.

24. A method for assessing susceptibility to stroke in an individual, comprising determining PDE4D isoform expression levels in the individual compared to control, wherein a difference in isoform expression is indicative of susceptibility to stroke.

25. The method of Claim 24 wherein isoform PDE4D7 and/or PDE4D9 expression is determined.

26. A method of diagnosing a susceptibility to stroke, comprising detecting an alteration in the expression or composition of a polypeptide encoded by phosphodiesterase 4D gene in a test sample, in comparison with the expression or composition of a polypeptide encoded by phosphodiesterase 4D gene in a control sample, wherein the presence of an alteration in expression or

composition of the polypeptide in the test sample is indicative of a susceptibility to stroke.

27. The method of Claim 26, wherein the alteration in the expression or composition of a polypeptide encoded by phosphodiesterase 4D gene comprises expression of a splicing variant polypeptide in a test sample that differs from a splicing variant polypeptide expressed in a control sample.

28. A method for preventing the occurrence of stroke in an individual in need thereof, comprising regulating a PDE4D isoform level compared to control, whereby the regulated isoform level mimics the level in a healthy individual.

29. The method of Claim 28 wherein isoform level is regulated by regulating expression of the isoform using a phosphodiesterase 4D gene binding agent, a phosphodiesterase 4D gene receptor, a peptidomimetic, a fusion protein, a prodrug, an antibody or a ribozyme.

30. The method of Claim 28 wherein the isoform level is controlled by genetically altering the isoform's expression level.

31. The method of Claim 28 wherein the isoform level is regulated by altering the ratio of isoforms.

32. The method of Claim 28 wherein isoform PDE4D7 and/or PDE4D9 is regulated.

33. A method for monitoring the effectiveness of treatment on the regulation of expression of one or more PDE4D isoforms at the RNA or protein level, or its enzymatic activity by measuring PDE4D message or protein or enzymatic activity in a sample of peripheral blood or cells derived thereof.

34. A method for predicting the effectiveness of a given therapeutic for stroke prevention or treatment in a given individual comprising screening for the presence or absence of the stroke at-risk haplotype in the phosphodiesterase 4D gene.

35. A method for predicting the effectiveness of a given therapeutic for stroke prevention or treatment in a given individual comprising screening for the expression of one or more PDE4D isoforms at the RNA or protein level, or its enzymatic activity by measuring PDE4D message or protein or enzymatic activity in a sample of peripheral blood or cells derived thereof.

36. A method of diagnosing a reduced or protective susceptibility to a stroke in an individual, comprising screening for a protective haplotype in the phosphodiesterase, 4D gene that is more frequently present in an individual compared to an individual susceptible to stroke, wherein the protective haplotype decreases the risk of stroke significantly

37. A method of Claim 36 wherein the protective haplotype is characterized by the A allele at position 142780, relative to SEQ ID NO: 1and allele -8 for microsatellite marker AC0088181-1.